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Review

Antimicrobial properties of plant barks as a natural strategy to reduce antimicrobial resistance- A narrative review

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ABSTRACT:

Introduction: Antimicrobial resistance (AMR) is both a rapidly growing and a major global threat to public health. AMR reduces the efficacy of existing antibiotics, increasing both the morbidity and mortality of infections as well as the cost of healthcare. Plants produce diverse bioactive secondary metabolites, some of which are obtained from the bark of plants and are thus an alternative source for the development of new antimicrobial drugs. **Methods:** A systematic narrative review was conducted of studies retrieved from electronic databases such as PubMed, PubMed Central, Scopus, and Web of Science, using Boolean search strings to identify antimicrobial activity of bark plant extracts published between 2015 and 2025. **Results**: We screened 40 studies based on PRISMA protocol and included them for qualitative analysis. Plant barks contain phytochemicals of different classes with the most abundant class being phenolic compounds, followed by terpenoids, alkaloids, and saponins. These compounds are broad-spectrum antimicrobial agents that work by various mechanisms including disruption of the membrane, inhibition of cell wall biosynthesis, inhibition of protein synthesis, inhibition of nucleic acid synthesis, enzyme inactivation and efflux pump inhibition. The compounds were found to be active against MDR *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae* and Candida *albicans* with MIC values ranging from very strong to medium levels of inhibition. Others have shown *in vivo* wound healing ability and systemic antimicrobial activity. Some methods of extraction have included microwave-assisted extraction and supercritical fluid extraction to maximize yield. **Conclusion:** The results of this review suggest that plant bark extracts are promising sources of multi-targeting antimicrobial candidates against resistant pathogens and further mechanistic, standardization, and clinical studies are warranted toward their translation into the clinic.

KEYWORDS: Antimicrobial activity, Antimicrobial resistance, Natural products, Phytochemicals, Plant barks.

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1. INTRODUCTION

The global burden of antimicrobial resistance (AMR) on public health, economic and food security is growing. [1] Conventional antibiotics continue to be ineffective against multidrug-resistant (MDR) bacteria and fungi, leading to increased morbidity and mortality as well as costs incurred by treating patients with resistant pathogens. [2][3] This calls for an immediate and on-going search of new antimicrobial agents from different sources. Natural products, especially from customary medicinal plants, always provide new opportunities as an established source of drug discovery that can be developed into novel therapeutic strategies. [4]

In this respect, barks (i.e. the outermost layers of protection from trees and woody plants) are particularly exciting, as they are most exposed to microorganisms, insects and environmental stresses, having amassed over the years and through evolution a tremendous diversity of secondary metabolites, with a variety of biological functions including strong antibacterial activity. [5][6]

This review seeks to provide a consolidated overview of the spectrum of claimed antimicrobial activity of different plant extracts of bark, the profile of active phytochemicals in each of the extracts, the mechanisms of action, plant species with most prominent antimicrobial activity, methodologies to evaluate antimicrobial activity, limitations for immediate clinical application, and future perspectives of translating plant bark extract-derived molecules into therapeutics to combat the growing global burden of infectious diseases and antibiotic resistance.

2. METHODOLOGY

An electronic literature search was conducted on the PubMed, PubMed Central and Scopus databases for the last 10 years using Boolean operators AND, OR, NOT, with limiters of English language, year of publication, and peer-reviewed journals. Only recent and quality articles were selected and considered after review and citation. Table 1 shows the search strategy applied in this narrative review. The final literature search was completed on 15 June 2026 in PubMed, PubMed Central, Scopus, and Web of Science databases.

Table 1: Search strategy

Database	Search Terms Used	Filters Applied	Results Retrieved	Notes
PubMed (via MEDLINE)	("Plant bark" OR "Stem bark") AND ("Phytochemicals" OR "Phenolic compounds" OR "Alkaloids") AND ("Antibacterial" OR "Antifungal")	Language: English; Publication years: 2015–2025; Peer-reviewed	120	Title/Abstract/ Keywords
PubMed Central (PMC)	("Bark extracts" AND "Bioactive compounds") AND ("Antimicrobial activity" OR "Anti-biofilm")	Language: English; Publication years: 2015–2025; Free full-text articles	95	Title/Abstract/ Keywords
Scopus	("Medicinal plants" OR "Bark-derived phytochemicals") AND ("Antimicrobial mechanisms" OR "Pathogen inhibition")	Language: English; Publication years: 2015–2025; Peer-reviewed	135	Title/Abstract
Web of Science	"Microbial resistance" OR "Drug resistance"	Language: English; Publication years: 2015–2025; Peer-reviewed	45	Title/Abstract/ Keywords

Study selection and screening process: The literature search retrieved a total of 375 records from electronic databases, including PubMed via MEDLINE (n = 120), PubMed Central (PMC) (n = 95), Scopus (n = 135), and Web of Science (n = 45). After removal of duplicates and records excluded for other reasons (n = 50), 345 records remained for title and abstract

screening. Following the initial screening, 135 records were excluded, leaving 210 reports assessed for retrieval. Of these, 30 reports could not be retrieved. A total of 180 full-text articles were assessed for eligibility, and 125 studies were excluded due to not meeting inclusion criteria, lack of phytochemical analysis, lack of focus on bark, absence of antimicrobial relevance, or insufficient experimental/mechanistic detail. Ultimately, 55 studies were included in the final qualitative synthesis. The study selection process is presented in accordance with PRISMA-style guidelines and is depicted in Figure 1.

Inclusion criteria: Studies in English between 2015 and 2025 in peer-reviewed journals were searched and primary articles, review and/or meta-analysis articles were selected for inclusion. Only plant bark and plant stem bark extracts with phytochemical characterization of phenolic compounds, tannins or alkaloids were analyzed and extracted for this review study. Articles were also included if they discussed the antibacterial, antifungal, or anti-biofilm activity, or the mechanisms of action or therapeutic potential of phytochemicals derived from the bark.

Exclusion criteria: Non-English studies, non-peer-reviewed studies, conference abstracts, editorials and letters were not included. Studies were excluded if they did not conduct any phytochemical analysis, were not microbiologically related to antimicrobial activity, or did not investigate bark (i.e. focused on other plant components e.g. leaves, roots etc., rather than the bark). We limited literature to 2015-2025 to consider current knowledge and advances in the field related to phytochemical and antimicrobial studies, potentially including studies with higher methodological quality and excluding outdated information. To validate the included literature, studies were also excluded for being duplicate or lacking sufficient experimental or mechanistic details of their findings.

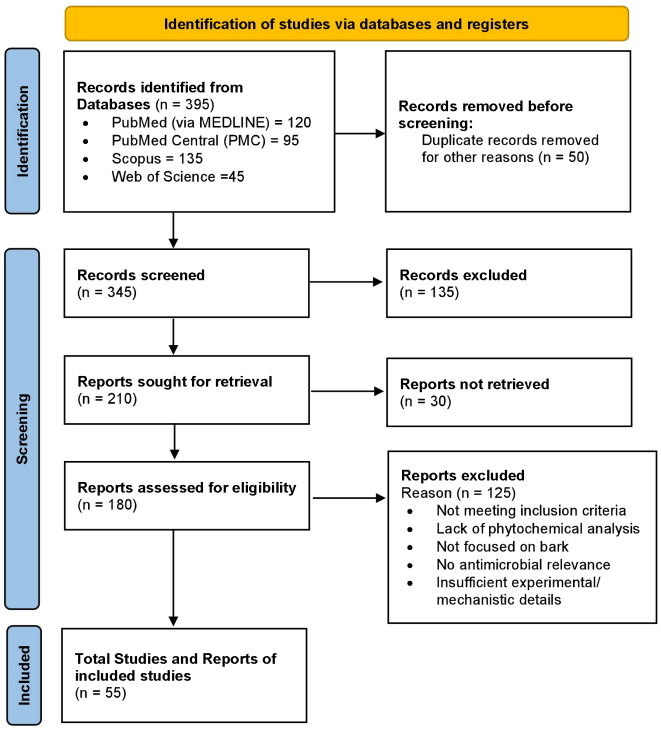

Figure 1: PRISMA flow diagram

Phytochemical diversity of plant barks, their antimicrobial components and their extraction processes.

Phytochemistry of plant barks: The tree's bark is an important chemical reservoir, comprising 9% to 15% of the tree's overall volume. [7] Bark, which acts as the first line of defense in woody vascular plants, contains a large amount of secondary metabolites, such as polyphenols, tannins, triterpenes, and suberinic acids. [8] The phytochemicals found in most abundance are phenolic derivatives (50.8%), terpenoids (26.6%), and alkaloids (5.7%). [9] Recent research shows that woody barks are a much richer source of polyphenols than other parts of the plant and have powerful antioxidant, antimutagenic and antibacterial properties. [10]

Some bark chemicals act specifically, such as trans-cinnamaldehyde from *Cinnamomum zeylanicum*, which causes permeabilization of membranes and inhibition of ATPases in some sensitive bacteria. Willow (Salix) bark contains catechol and salicin derivatives that cause membranous instability and electrolyte leakage among resistant bacteria. [12] *Syzygium*

cumini bark contains tannins that have high bactericidal activity because of their ability to destabilize bacterial membranes. [13] These effects are attributable to diterpenoids and quercetin in *Azadirachta indica*. [14] *Albizia lebbeck* and other species have been reported to have saponins which compromise the integrity of cell walls. [15] The chemodiversity of plant barks highlights their potential in developing biocompatible therapeutics against MDR. [16]

Extraction technology: Plant bark has a complex structure comprised of lignocellulosic material and requires advanced technologies for higher yields of extractable bioactive compounds. Conventional solvents used in extraction have been replaced with newer "green" technologies which can have higher selectivity and lower environmental impact. [17, 8] Simultaneous microwave-ultrasound assisted extraction is a recent development that shows a synergetic effect and a meaningful increase in the extraction of natural antioxidants. [7] Supercritical fluid extraction and subcritical water extraction are also very efficient methods to yield thermolabile compounds, free from toxic solvent residues. [18] Organosolv and subcritical water technologies are in the heart of modern biorefinery models, which allow the sequential valorization of extracts and solid residues into bio-based products fit for use much more efficiently than conventional technologies. [8] Further optimization of the extraction processes through the use of polar solvents, high temperatures close to the boiling point, and short extraction times is necessary to achieve the maximum total phenolic content and extraction efficiency and thus enable the incorporation of bark extraction in circular bioeconomy processes. [19, 8]

Table 2. Phytochemical classes in plant bark and antimicrobial activity

Class	Key compounds	Antimicrobial activity (with refs)
Phenolics	Flavonoids, tannins, phenolic acids, lignans, stilbenes	Broad antibacterial and antifungal activity; inhibit enzymes, nucleic acid synthesis, efflux pumps and biofilms (*Candida spp*.) [20,21]
Terpenoids	Mono-, sesqui-, di-, triterpenes	Antibacterial and antifungal effects; includes fungicidal triterpenes in bark extracts [22,23]
Alkaloids	Nitrogen-containing compounds	Inhibit peptidoglycan synthesis and fungal cell wall integrity; broad antimicrobial action [24]
Saponins	Glycosidic surfactants	Disrupt fungal membranes via sterol interaction; inhibit biofilm and yeast–hyphal transition [25]
Synergistic action	Mixed phytochemicals	Combined multi-target effects enhance overall antimicrobial potency [22]

3. Mechanisms of antimicrobial action exhibited by plant bark extracts

Plant phytoconstituents and extracts induce antimicrobial activities by a few commonly independent and/or colligated mechanisms in the microorganisms tested. In most cases, the plant phytoconstituents target more than one cellular pathway in the microorganisms (Figure 2). A multi-target approach may also provide a useful strategy for overcoming resistance to single-target synthetic agents. [1,4] The main mechanisms for this include:

Disruption of cell membranes: Phytochemicals such as phenolic compounds and certain terpenoids can act on microbial plasma cell membranes, thus changing their permeability. The permeability change causes the leakage of some intracellular constituents (i.e., ions, ATP, nucleic acids, etc.) and metabolic dysfunction, which leads to their death. [26] Key properties affecting the activity of the membranes include their lipophilicity that allows their intercalation into the lipid bilayer.

Inhibition of cell wall synthesis: selected compounds of bark can inhibit the synthesis and assembly of integral constituents of the bacterial (peptidoglycan) or fungal (chitin, glucans) wall; without its support or integrity, bacteria or fungi are prone to osmotic lysis and other adverse conditions. [26] In fungi, alkaloids may inhibit peptidoglycan. [25]

Inhibition of protein and/or nucleic acid synthesis: Many phytochemicals inhibit cellular processes such as protein synthesis (by

disrupting ribosomes or translation factors) or the synthesis of nucleic acids. [5] For example, tannins inhibit the synthesis of nucleic acids.

Enzyme inactivation: Secondary plant metabolites can bind to and inactivate microbial enzymes directly or indirectly. They must be involved in one or more metabolic pathways, virulence factors or cell maintenance for the blocking of biochemical pathways necessary for microbial reproduction and growth. [27]

Efflux pump inhibitors (EPI): Microorganisms can evade the effects of antibiotics via efflux pumps that extrude them from the cell. Some compounds found in plant bark can inhibit these pumps and restore, or increase, the activity of customary antibiotics, or their own antimicrobial activity. [1] For example, flavonoids have been shown to inhibit fungal efflux pumps. [25]

Experimental mechanisms of action determined for bark extracts by *in vitro* studies include disruption of cell membranes, inhibition of cell wall synthesis, inhibition of protein and nucleic acid synthesis, enzyme inactivation and disruption of biofilm formation, and inhibition of efflux pumps. Theoretical mechanisms of action inferred by computational modeling, molecular docking studies, or by analogy to other studies include disruption of quorum sensing, multi-target synergism and modulation of virulence- and resistance-associated genes. These hypotheses warrant further study, including validation through microbiology studies and translational studies to establish their biological importance, effect *in vivo*, and possible utility against antimicrobial-resistant pathogens.

Molecular mechanism: At the molecular level, plant bark extracts impact the growth of microbes through wide-ranging transcriptional reprogramming. RNA-sequencing-based transcriptomics resulted in differential regulation of genes, including down-regulation of peptidoglycan biosynthesis, and inhibition of DNA replication that interfere with cell wall biosynthesis and cell division in bacteria. [28] These extracts also induce DNA replication stress, genomic DNA destruction, and the downstream inhibition of enzyme and receptor synthesis. [29] The extracts also up-regulate RNA decay and oxidative phosphorylation, two typical markers of metabolic depletion. [28] Phytochemicals can also regulate gene expression, inhibit efflux pump pathway ATPases and interfere with the cellular signaling pathway on a molecular level. [16]

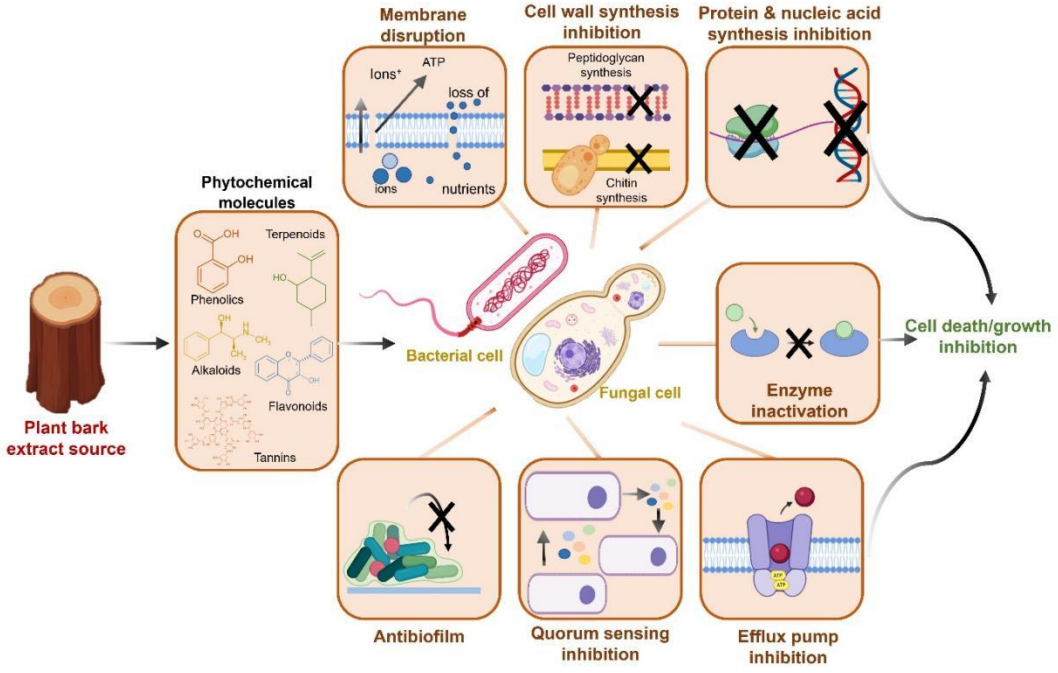

Figure 2: Mechanism of plant bark against microbes

4. Selected plant species and their antimicrobial bark activity

Antimicrobial studies on various plant extracts prepared from bark, with *in vitro* and *in vivo* models, including the methanol, ethanol, aqueous, hydroethanolic, dichloromethane and 80% methanol extracts of the bark, have been documented. Most of the studies included here have been carried out under *in vitro* conditions and were the primary mode of screening for antimicrobial activity. For example, 80% methanolic bark

extracts of *Clerodendrum englerianum*, *Euphorbia depauperata*, *Lippia adoensis*, *Dombeya penninervium*, and *Rumex abyssinicus*, as well as aqueous extracts of *Bridelia ferruginea*, and hydroethanolic extracts of the plants *Sorindeia madagascariensis* and *Albizia harveyi* were used in *in vitro* screening, which demonstrated that extracts obtained with different solvent systems can be useful for obtaining bioactive antimicrobial agents. In this context, methanolic extracts obtained from the bark of *Phellodendron* spp. and *Mangifera indica* were screened *in vitro*, showing the importance of using polar organic solvents for isolating the antimicrobial phytochemicals of interest. [33, 34]

A few *in vivo* studies on animals or wounds, also give these plants a more translational origin as antimicrobial agents, and include *Anogeissus leiocarpa*, *Bridelia ferruginea*, *Prunus africana*, *Cinnamomum zeylanicum*, *Alstonia scholaris*, *Saraca asoca*, *Ficus racemosa*, Symplocos racemosa and *Azadirachta indica*, most of which are trees, and a few others shrubs. [35]

***In vitro* antimicrobial activity against bacterial and fungal pathogens:** *In vitro*, bark extracts were demonstrated to have strong antimicrobial activity against a number of bacterial and fungal pathogens. Methanolic and aqueous extracts of bark had strong activity against *methicillin-resistant S. aureus* (MRSA *S. aureus*), *methicillin-susceptible S. aureus*, *Streptococcus pyogenes*), and *Streptococcus mitis*. *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*K.* Phytochemical screening and *in vitro* antibacterial activity against pathogenic bacteria were evaluated. *Clerodendrum englerianum* inhibited growth of MRSA and *S. pyogenes* with the smallest concentration of the extract that inhibited growth (MIC) values in the range of 1.0 to 128.0 µg/mL, and similar values were noted for *Euphorbia depauperata* against *E. coli* and *K. pneumoniae*.

Two more, *Lippia adoensis* and *Dombeya penninervium*, had antifungal and antibacterial activity like that of *R. abyssinicus* against *C. albicans*, *Trichophyton rubrum* (*T. rubrum*), and *Klebsiella pneumoniae* (*K. pneumoniae*) with MICs (minimal inhibitory concentrations) of up to 512.0 µg/mL. *R. abyssinicus* was also shown to have an effect on MRSA and *C. albicans*. [30]

Aqueous extracts of the bark of *Bridelia ferruginea* showed activity against *B. cereus and S. aureus* at an MIC of 25.0 mg/mL. Hydroethanolic extracts of *Sorindeia madagascariensis* and *Albizia harveyi* inhibited *S. aureus, P. aeruginosa*, *Salmonella Typhi* (*S. typhi*) and *C. albicans*. [31, 32] Methanol extraction of *Phellodendron* species showed moderate inhibition of *S. aureus* and *E. coli*, measuring 256.0 µg/mL, [33] while *Commiphora* spp. showed inhibition of *Mycobacterium* with MIC ranging from 0.39 to 9.35 mg/mL depending on the solvent system used for extraction. [36]

Terminalia arjuna and *Cinnamomum zeylanicum* ethanol extract possess zone of inhibition against *S. aureus*, *S. epidermidis*, *K. pneumoniae* respectively which indicates promising antibacterial activity. [37, 38] The methanol bark extract of Mangifera indica also showed good activity with an MIC value ranging from 3.125 - 6.25 µg/mL against the tested strains of Gram-positive and Gram-negative bacteria. [34]

Antimicrobial and therapeutic efficacy *in vivo:* *In vivo* tests have shown activity of extracted barks on various animals and on wound healing. *Anogeissus leiocarpa* bark has shown *in vivo* antibacterial activity against *E. coli* with an oral dose of 69.44 mg/kg. [35] Antimicrobial properties of *Bridelia ferruginea* aqueous extract were also dose-dependent in the animal study (*S. aureus* and *E. coli* at 50-100 mg/kg). [39]

In wound healing models, antimicrobial and wound healing effects were exhibited by *Prunus africana* which showed 100% of the wounds being healed in 18 days on infected models and reflected the pronounced synergism of such effects. [40] In *Proteus mirabilis* infections, the *Cinnamomum zeylanicum* aqueous extract exhibited antimicrobial activity with organ protective effects. [41] *Alstonia scholaris* also improved the survival rate of animals infected with *Streptococcus*. [42]

Other plants with important contraction and antimicrobial-associated wound healing (in infected wound model), *Saraca*

asoca, *Ficus racemosa*, *Symplocos racemosa* and *Azadirachta indica*, corroborate customary claims of using these plants for skin infections. *Cinnamomum zeylanicum* was a part of several aqueous formulations that promoted important wound healing, suggesting it has high sustained *in vivo* antimicrobial activity. [43]

Table 3: Antimicrobial activities of various bark extracts

S.No	Plant species	Extract type	Study type	Target microorganisms	Antimicrobial activity	Reference
1	*Clerodendrum englerianum*	80% Methanol	*In vitro*	*MRSA*, *S. pyogenes*	MIC: 1.0–128.0 μg/mL	[30]
2	*Euphorbia depauperata*	80% Methanol	*In vitro*	*E. coli*, *K. pneumoniae*	MIC: 4.0–128.0 μg/mL	[30]
3	*Lippia adoensis*	80% Methanol	*In vitro*	*S. pyogenes*, *C. albicans*	MIC: 16.0–512.0 μg/mL	[30]
4	*Dombeya penninervium*	80% Methanol	*In vitro*	*T. rubrum*, *K. pneumoniae*	MIC: 8.0–128.0 μg/mL	[30]
5	*Rumex abyssinicus*	80% Methanol	*In vitro*	*MRSA*, *C. albicans*	MIC: 16.0–128.0 μg/mL	[30]
6	*Bridelia ferruginea Benth*.	Aqueous	*In vitro*	*Bacillus cereus*, *S. aureus*	MIC: 25.0 mg/mL	[31]
7	*Sorindeia madagascariensis*	Hydroethanolic	*In vitro*	*S. aureus*, *P. aeruginosa*	Significant MIC/MBC	[32]
8	*Albizia harveyi*	Hydroethanolic	*In vitro*	*S. typhi*, *C. albicans*	Potent antimicrobial action	[32]
9	*Phellodendron* spp.	Methanol	*In vitro*	*S. aureus*, *E. coli*	MIC: 256.0 μg/mL	[33]
10	*Commiphora mildbraedii*	Methanol	*In vitro*	*Mycobacterium* spp.	MIC: 0.39–9.35 mg/mL	[36]
11	*Commiphora edulis*	Dichloromethane	*In vitro*	*Mycobacterium* spp.	MIC: 1.56 mg/mL	[36]
12	*Commiphora ellenbeckii*	Aqueous	*In vitro*	*Mycobacterium* spp.	MIC: 3.125 mg/mL	[36]
13	*Terminalia arjuna* Wight & Arn.	Ethanol	*In vitro*	*S. aureus*, *K. pneumoniae*	ZOI: 15.0–15.5 mm	[37]
14	*Cinnamomum zeylanicum* Blume	Ethanol	*In vitro*	*S. aureus*, *S. epidermidis*	ZOI: 18.44–19.22 mm	[38]
15	*Mangifera indica* L.	Methanol	*In vitro*	*S. aureus*, *E. coli*	MIC: 3.125–6.25 μg/mL	[34]
16	*Anogeissus leiocarpa*	Ethanol	*In vivo*	*E. coli*	Oral dose: 69.44 mg/kg	[35]
17	*Bridelia ferruginea Benth*.	Aqueous	*In vivo*	*S. aureus*, *E. coli*	Dose: 50.0–100.0 mg/kg	[39]
18	*Prunus africana* (Hook.f.) Kalkman	80% Methanol	*In vivo*	Wound pathogens	100% closure by day 18	[40]
19	*Cinnamomum zeylanicum* Blume	Aqueous	*In vivo*	*Proteus mirabilis*	Kidney tissue recovery	[41]
20	*Alstonia scholaris* R. Br.	Aqueous	*In vivo*	*Streptococcus* species	Increased animal survival	[42]
21	*Saraca asoca (Roxb.)* Wilde	10% Aqueous	*In vivo*	Wound pathogens	Significant wound contraction	[43]
22	*Ficus racemosa* L.	10% Aqueous	*In vivo*	Wound pathogens	High healing efficacy (Gupta et al., 2020)	[43]
23	*Symplocos racemosa* Roxb.	5% Aqueous	*In vivo*	Wound pathogens	Significant healing action	[43]
24	*Azadirachta indica* A. Juss.	5% Aqueous	*In vivo*	Wound pathogens	Verified antimicrobial healing	[43]
25	*Cinnamomum zeylanicum* Blume	5% Aqueous	*In vivo*	Wound pathogens	Therapeutic wound closure	[43]

5. Antimicrobial resistance

Membrane perturbation mechanism of plant barks against MDR/XDR pathogens: There is strong evidence that plant bark extracts can interfere with AMR through disruption of the bacterial membrane of MDR/XDR pathogens. For instance, the bark extract of Acacia nilotica has shown activity against MDR *E. coli* and *Salmonella* by disrupting the membrane and causing intracellular leakage of proteins and nucleic acids. Extracts of Terminalia arjuna are effective against the MDR *S. aureus* through disruption of the membrane by its phenolic and tannin constituents [45], whereas *Salix alba* induces membrane destabilization and electrolyte leakage from pathogenic *S. aureus* bacteria. [12] *Syzygium cumini* showed strong antibacterial activity against MDR *E. coli* due to tannin-mediated membrane destabilization. [13] Supporting this idea, targeting membranes may be a promising strategy against AMR organisms.

Resistance modulation in the MDR/XDR bacteria by inhibiting metabolism and efflux pumps: Numerous bark extracts have been identified to exhibit AMR-modulating activity by inhibiting bacterial energy metabolism and efflux processes, confirming the involvement of energy processes in forming AMR. *Cinnamomum zeylanicum* demonstrated activity against MDR/XDR *Mycobacterium tuberculosis* by inhibiting membrane-bound ATPases, leading to a loss of energy coupling. [11] *Mangifera indica* is known to be a resistance modifier in MDR S. aureus, reducing the pumping of protons by H^+-ATPase and, thus, increasing susceptibility. [46] *Holarrhena* antidysenterica is another resistance modifier in MDR/XDR *Pseudomonas aeruginosa* (*P. aeruginosa*) in which conessine, an alkaloid, restores susceptibility by inhibiting the MexAB-OprM efflux pump in the organism. [47]

Attenuation of clinical resistance through growth and virulence suppression: Plant bark extracts may exhibit an AMR effect by inhibiting the growth of bacterial cells and virulence factors. The extract of *Azadirachta indica* exhibited this effect against clinically resistant *K. pneumoniae* with diterpenoids and quercetin inhibiting its growth. [14] *Saraca asoca* disrupts the metabolic pathways of clinical isolates of *P. aeruginosa*, affecting drug resistance and adaptation. [48] *Albizia lebbeck* inhibits the growth of MRSA by inhibiting nucleic acid synthesis and disruption of the cell wall using saponins. [15] Together, these activities lead to a loss of bacterial fitness under antibiotic-selective pressure and AMR detainment.

6. Standardized tests were employed to assess the antimicrobial activity of the bark extracts.

Standardized *in vitro* and, more recently, *in vivo* methods have been developed to properly describe the antimicrobial activity of plant bark extracts (Figure 3), which have been used to characterize the potency, spectrum of activity and concentration-value relationships of extracts and isolated compounds.

Conventional susceptibility testing

Method of diffusion disc: The simplest and qualitative method of detecting the antimicrobial effect consists of placing discs impregnated with the test extract on a plate with a culture of the target microorganism. The basal zone of inhibition observed around the disc is a reflection of the antimicrobial activity. It identifies activity rapidly from the start. [12] [49]

Agar well diffusion: This test is essentially the same as the disc diffusion test, except wells are cut into the agar and the extract is added to the wells. This is used during the primary screening and allows larger volumes of extract to be tested. [49]

Broth microdilution method: This quantitative methodology is the gold standard for the determination of MIC/MBC/MFC. The extract is serially diluted in the broth in culture tubes (or microtiter plates), inoculated with the microbe to be tested in a fixed-age suspension, and incubated. MIC and MBC/MFC endpoints are defined as the lowest concentration that visibly inhibits and kills at least 99.9% of the starting inoculum, respectively. [12] The use of a growth-inhibiting redox indicator such as the dye p-iodonitrotetrazolium violet (INT) improves

visualization of microbe growth. MIC values of 625 µg/mL or lower have typically, although not always very conservatively, been interpreted to correlate with antibacterial activity of moderate or better. [50]

Time-kill assays determine the extent and speed of killing of microbes by an antimicrobial agent over a fixed period of time. These tests can be performed to determine whether the agent is bactericidal (killing the bacteria).

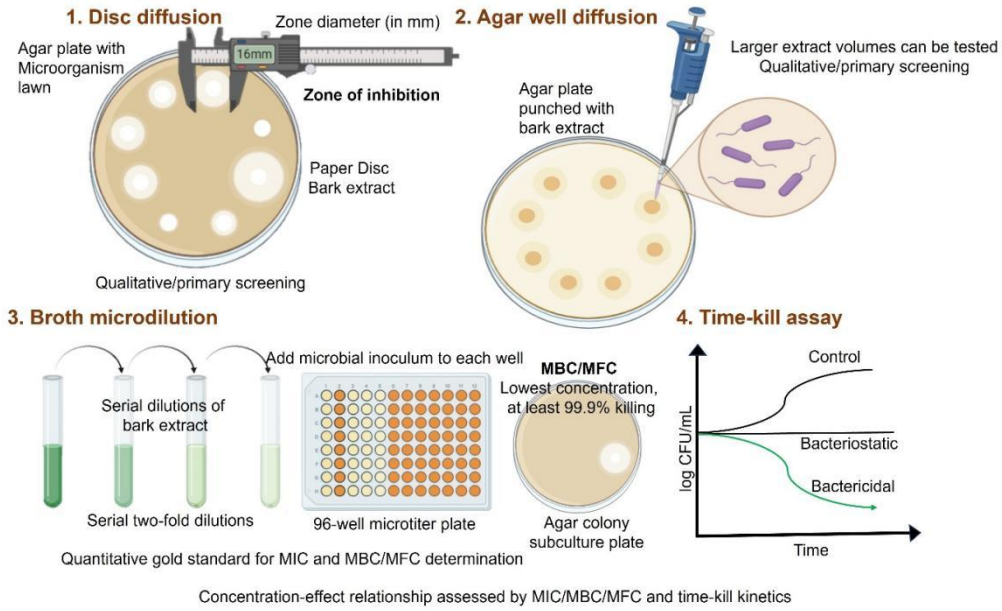

Figure 3: Different methods used to assess the microbial activities in the plant bark. 1. Disc diffusion 2. Well diffusion 3. Broth microdilution and 4. Time-kill assay

Specialized Assays: Biofilm-related bioassays: Biofilms are involved in chronic infections. Optimized assays are used to quantify inhibition of biofilm formation or biofilm removal. Bioassays can measure biofilm mass with the crystal violet assay of biomass by staining adhered cells. Other bioassays use microscopy to measure biofilm formation and cell viability with staining techniques.

The anti-quorum sensing activity of extracts can also be measured in reporter strains (e.g., *Chromobacterium violaceum*), which only ferments upon quorum sensing dependent expression of violacein, the colored pigment of the bacterium. Quorum sensing inhibitors inhibit violacein biosynthesis, thereby exhibiting anti-quorum sensing activity. [51]

Efflux pump inhibition assay to screen for the ability of the tester extract to sensitize resistant strains by inhibiting efflux pumps is done by comparing the MIC of an antimicrobial in the absence and presence of (removed) the test extract or known efflux pump inhibitor. [52]

Cytotoxicity assays: For bark extracts, cytotoxicity on eukaryotic cells (e.g. cell lines of human origin) will be assessed by MTT assay and hemolysis assay before any *in vivo* administration is performed. Such assessments serve as the basis for determining therapeutic index of a treatment and its possible adverse effects. [53]

All of the above can allow researchers to investigate the potential of plant bark extracts as a source of antimicrobial compounds and find candidates for future development.

7. Challenges and limitation

Isolation and characterization of bioactive compounds: the compounds in the crude extract may act collectively to have the observed antimicrobial activity, thus isolation and

characterization of active compounds is critical to obtain a better understanding of mechanisms of action, increasing the efficacy as a drug and for drug development purposes. [51] A complex array of chromatographic techniques and structural elucidation is employed.

Problems with standardization: One of the main limitations in developing bark-based antimicrobial agents for clinical use is the challenge of standardization, as plant bark is a complex chemical substance, with its phytochemical composition usually depending on its exact species or botanical variety, geographical area, time of harvest, climate conditions, and extraction method. Slight changes in solvent type, extraction process time, or temperature can result in differing concentrations of bioactive constituents, poorly reproducible batches, and a recommended dose that varies according to each extract. This obstructs the establishment of a standard profile of the extract and makes pharmacological and regulatory validation difficult.

Toxicology and safety: Despite promising antimicrobial activity exhibited by bark extracts *in vitro*, safety and toxicity of such materials are not fully characterized. At relatively high concentrations and/or prolonged exposure times, phytochemicals extracted from bark may exhibit concentration-dependent toxicities including cytotoxic, hepatotoxic, nephrotoxic, and neurotoxic activities, among others. Also, interactions between putative multiple constituents of crude extracts (synergistic or antagonistic) may affect toxicity. This means that the determination of safe doses for therapeutic use in humans requires detailed toxicological studies (acute, sub-acute and chronic tests in appropriate *in vivo* animal models).

Pharmacokinetics and bioavailability: The pharmacological potential of phytochemicals in bark is frequently restricted by poor pharmacokinetic properties. Many bioactive constituents are poorly soluble in water, poorly absorbed in the intestine, subject to important first pass metabolism, or rapidly cleared from the systemic circulation. Thus, despite the potential for good *in vitro* antimicrobial activity, the concentration of drug that is achieved *in vivo* may not be sufficient to attain a therapeutic concentration. Strategies to overcome this limitation include nanoparticles, liposomal formulations, the use of prodrugs, and optimization of the structure of the antimicrobial to improve absorption, stability, and retention [54,55].

Clinical trial requirements and translational challenges: Successful transition of preclinical data to approved antimicrobial agents requires a rigorous, multi-staged, and expensive evaluation focused on the safety, efficacy, dosage, and side effects of the agent in humans. The process is time-consuming and highly regulated, greatly increasing costs before receiving regulatory approval. Clinical failure of Phase I clinical trials, due to insufficient efficacy or undiscovered toxicity that was not predicted by preclinical models, limits the success of translating the results of basic research into new medicines.

Intellectual property and biopiracy: The development of therapeutics from medicinal barks has faced issues surrounding intellectual property rights and biopiracy. Traditional medicinal knowledge that is passed down in indigenous communities has historically led to the discovery of bioactive plant species for medicinal use. Despite this, equitable sharing of benefits and recognition of source communities remain concerns, with international instruments such as the Nagoya Protocol on Access and Benefit Sharing of Genetic Resources focusing on fair and equitable sharing of benefits, formal documentation, ethical acquisition and development, and lawful use.

Future research directions: Future studies on the antimicrobial activity of plant bark extracts should target those in-between the bench and the bedside. As shown in the current review, most of the reported activity has been obtained from *in vitro* studies, with a limited amount of information from *in vivo* studies and no results on human clinical studies. Future studies should stress: standardization of extraction protocols, improving toxicity profiling and

pharmacokinetics/bioavailability assessment, establishing relevant preclinical models, and conducting multicenter human clinical trials and regulatory-guided evaluations of efficacy and safety to show therapeutic relevance in combating antimicrobial resistance. Such efforts will improve the advance from preclinical stages to clinical application. In addition, mechanistic investigations using omics technologies, imaging and *in vivo* infection models could be developed to validate molecular targets and synergistic effects proposed chiefly using computational and *in vitro* methods. This would help to accelerate the translation of promising antimicrobial agents from the bark of plants into clinical therapeutics for local and global areas where antimicrobial resistance is a highly important health issue.

8. CONCLUSION:

In this review, it is clear that plant bark extracts have important antimicrobial activity against a variety of pathogenic bacteria, including antibiotic resistant strains, as well as fungi. These activities can be linked to the presence of several phytochemicals, including phenolics, terpenoids, alkaloids and saponins. It is thought that the extracts exert their antibacterial effect by acting on multiple targets including cell membranes, bacterial cell wall synthesis, nucleic acids and proteins, enzymes and efflux pumps. However, although there is substantial *in vitro* evidence, there is little *in vivo* evidence and virtually no clinical evidence of these properties. Therefore the findings are preclinical. Standardization, variation in extraction procedure, lack of pharmacokinetics data and concern regarding safety must be adequately addressed for clinical translation. Future work must investigate detailed toxicology studies, mechanism of action studies as well as conducting clinical trials, for developing natural products as powerful therapeutic agents against antimicrobial resistance at a global level.

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